CASE REPORTS

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Staphylococcal Myositis in a Compromised Host

Successful Treatment with the Synergistic Combination of Nafcillin and Gentamicin

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HEMATOLOGIC MALIGNANCIES and their treatment result in hypersusceptibility to many infectious agents as a consequence of suppression of normal host defense mechanisms. A severe staphylococcal infection, resembling tropical myositis, developed in a patient with myelomonocytic leukemia. Recovery followed treatment with nafcillin and gentamicin, a combination shown to be synergistic against the Staphylococcus aureus isolated from this patient.

Report of a Case

A 30-year-old black man was admitted to the University of California (Davis)-Sacramento Medical Center (UCD-SMC) with a one day history of bilateral thigh and arm pain, and fever. One year previously, he had been seen at UCD-SMC because of malaise, fatigue and dyspnea on exertion. Hepatosplenomegaly and pancytopenia were found; findings on bone marrow biopsy, lymph node biopsy and ferrokinetic studies were consistent with a myeloproliferative disorder, but of unknown type. Subsequently, a diagnosis of myelomonocytic leukemia was made. Hemoglobin type was AA, serum immunoglobulin levels were normal, and reactions to both intermediate purified protein derivative (PPD) and mumps skin tests were negative. The patient was treated with prednisone, and a dose of 100 mg every other day was continued to the current admission. During this interval, the leukocyte counts were consistently low, ranging between 1,200 and 2,100 cells per cu mm.

On physical examination at admission to UCD-SMC, the patient appeared to be in a toxic condition. Temperature was 102°F (38.9°C), pulse rate was 150 beats per minute and blood pressure was 100/60 mm of mercury. Both thighs and arms were swollen, erythematous, warm and tender. The skin was intact and there was no evidence of peripheral embolization. Scleral icterus, a grade 2/6 systolic ejection murmur along the left sternal border and hepatosplenomegaly were present. Right lower quadrant tenderness and guarding were present; however, bowel sounds were normal. The hematocrit reading was 36; of 1,600 leukocytes per cu mm, 85 percent were lymphocytes and 15 percent were polymorphonuclear leukocytes. There were 25,000 platelets per cu mm. The creatine phosphokinase value was 2,000 units; the serum aldolase level was normal, and myoglobinuria was not detected. Six blood cultures and a culture of serosanguineous exudate aspirated from the left thigh yielded staphylococcus aureus which was shown to be resistant to penicillin G *in vitro*.

Treatment was begun with 250 mg of nafcillin per kg of body weight per day injected intravenously as six equal portions (3 gm) every four hours and 5 mg of gentamicin per kg of body weight per day injected intravenously as six equal

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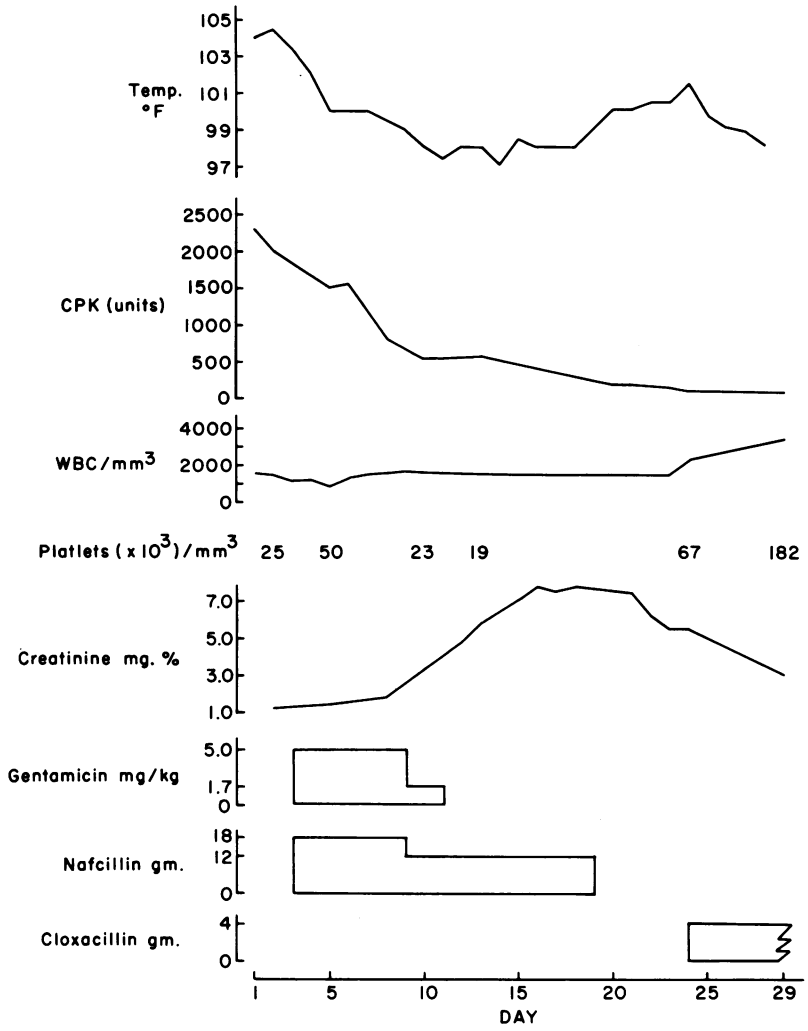

Figure 1.—Clinical course of the patient while at the Sacramento Medical Center. CPK=creatine phosphokinase.

portions (60 mg) every four hours. After six days, the dose of gentamicin was reduced to 1.7 mg per kg of body weight per day given intravenously as six equal portions (20 mg) every four hours. Because of a progressive rise in the serum creatinine (Figure 1), and because there had been resolution of the abdominal pain, muscle swelling, tenderness and fever, the gentamicin was discontinued and the nafcillin dosage was reduced to 2 gm every four hours for the remaining ten days of therapy. Hydrocortisone was given initially at a dose of 50 mg intravenously every six hours and was continued for 17 days at which time prednisone therapy was resumed. Fever returned three days after administration of nafcillin was stopped; therapy with cloxacillin—55 mg per kg of body weight per day given perorally as four equal portions (1 gram) every six hours—resulted in defervescence within two days. Cloxacillin treatment was terminated after ten days.

Antimicrobic Synergy

The bactericidal activity of different combinations of nafcillin and gentamicin against the strain of Staphylococcus aureus in this case was determined as described by Barry and Sabath.[1] Briefly, serial dilutions of each drug were prepared in Mueller-Hinton broth and combined in a two dimensional array. Each tube was inoculated with 10^5 colony forming units (CFU) per ml. After 18 hours of incubation, 10 percent of the volume of each tube without visible growth was subcultured on drug-free blood agar plates and the number of survivors calculated. Concentrations which resulted in a 99.9 percent reduction of viable units were accepted as minimal lethal concentrations (MLC) which are plotted as an isobologram (Figure 2). The straight line connecting the MLC for gentamicin alone with the MLC for nafcillin alone represents the MLC's ex-

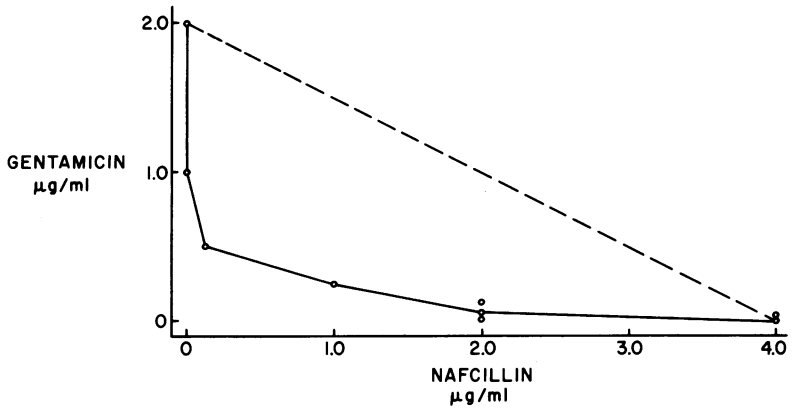

Figure 2.—Isobologram demonstrating the syngergistic effects of nafcillin and gentamicin in achieving a 99.9 percent reduction of viable Staphylococcus aureus. The dashed line shows the relationship expected for additive drug effects.

pected if these drugs were simply additive in effect. Because the MLC's of the combinations were in fact less than would be expected from addition, the combined action was synergistic. For example, a 99.9 percent bactericidal effect required 2 micrograms (μg) per ml of gentamicin or 4 μg per ml of nafcillin acting alone but was achieved with only 0.5 μg per ml of gentamicin and 0.125 μg per ml of nafcillin acting in combination.

Discussion

The manifestations of the illness in this case were strikingly similar to the clinical features of tropical myositis.[2-4] The distribution of acute inflammation to the large muscle groups of the thigh and upper arm in a febrile patient is characteristic and provided an important clue to the cause, and hence to treatment. Involvement of the right iliopsoas muscle was indicated by right lower quadrant pain and the tendency for the patient to lie with the right thigh partially flexed. This is a well described feature of tropical myositis and should not be confused with intraabdominal causes of right lower quadrant pain. The conditions that predispose to the development of the tropical disease are not clear although malnutrition, parasitic disease and trauma have been mentioned. "Tropical" pyomyositis, without serious underlying disease, may be seen in North America in persons who have recently arrived from tropical areas.[5] In the present case, it seems clear that the underlying hematologic malignancy and leukopenia were responsible for the fulminant myositis and bacteremia. A variety of clinical conditions that result in impaired host defenses have been associated with staphylococcal bacteremia; however, myositis has not been described as a clinical feature in these patents.[6]

Although the effect of antimicrobics on bacteria *in vitro* may be dramatic, the results of treatment are often decisively influenced by host defenses. This can be seen in diseases which involve local impairment of defenses, as in bacterial endocarditis. Mediators of host resistance either cannot reach the site of infection or are prevented from bactericidal action by the local environment, and the antimicrobics used in therapy must kill the infecting bacteria for success in treatment. General impairment of defenses, as in patients with congenital immunological deficiencies or chronic granulomatous disease, also renders successful treatment with antimicrobics more difficult. This is also true in patients with the acquired deficiencies which occur in myeloma, lymphoma and leukemia, and as a result of therapy with immunosuppressive drugs or with ionizing radiation. Despite the development of potentially bactericidal antimicrobics, the treatment of infections in granulocytopenic patients is often ineffective.[7] Unfortunately, there is little information on the extent to which antimicrobic treatment must be augmented when there is a particular defect in host defenses.

With some microorganisms the bactericidal effects of one antimicrobic are greatly enhanced in the presence of a second antimicrobic with a different mechanism of action. The classical example of this phenomenon is the synergistic action of penicillin and streptomycin against strains of enterococci;[8] this combination has been successfully applied to the treatment of enterococcal endocarditis.[9] Other examples of antimicrobic synergy are known,[10] including evidence for a synergistic effect *in vivo* of a penicillin and an aminocyclitol against Staphylococcus aureus.[11,12] The combination of penicillin G and gentamicin was found to be more effective than either anti-

microbic alone in the treatment of experimental staphyloccal infections in mice.[13] Because it was necessary to obtain the greatest possible bactericidal effect in this critically ill patient with leukopenia, a combination of nafcillin and gentamicin was used initially. As shown in Figure 2, the minimum lethal concentrations of combinations of these two antimicrobics were less than predicted by additive effects, confirming previous results with this combination against S. aureus.[14] It should be pointed out that some antimicrobic combinations have merely additive effects while others may be antagonistic.[15] For example, a deleterious clinical effect was shown in the treatment of pneumococcal meningitis with the combination of penicillin and chlortetracycline.[16]

A gratifying response to treatment was obtained in this case as shown in Figure 1. During the first week, the patient's temperature returned to normal and his general condition improved notably. There was extensive destruction of muscle, as evidenced by the serum creatinine phosphokinase level; although the concentration of the enzyme decreased rapidly, it did not become normal until the third week. Abscess formation requiring drainage, a characteristic feature of pyomyositis, did not occur in this patient with leukopenia. The creatinine clearance declined with a progressive rise in the serum creatinine level. Several factors may have been responsible.

It might be suspected that myoglobin released from damaged muscle could contribute to the renal impairment; however, the urine sediment was normal and myoglobinuria was not detected. Myoglobin has not been detected in the urine of patients with tropical myositis; however, tubular necrosis with oliguria does occur and has been related to the presence of dehydration and shock.[17] In our patient, hypotension and tachycardia were present for several days and it is likely that some degree of renal ischemia as well as gentamicin toxicity resulted in impaired renal function. Fever returned during the last week in hospital at which time a good response was obtained to orally administered cloxacillin, although S. aureus was not isolated again from cultures of the blood.

Clinical situations have been described in which impaired host defenses compromise the outcome despite treatment with antimicrobics. In such patients, it is necessary to obtain maximum bactericidal effects for prolonged periods to effect a cure. Although our patient might have recovered with use of nafcillin alone, the presence of leukemia with leukopenia and a rapidly progressing staphylococcal infection, prompted vigorous application of a potentially synergistic combination of antimicrobics. Rational combinations of antimicrobics may have a place in therapy when there is severe impairment of host defenses.

REFERENCES

1. Barry AL, Sabath LD: Special tests: Bacterial activity and activity of antimicrobics in combination, *In* Lennette EH, Spaulding EH, Truant JP (Eds): Manual of Clinical Microbiology, American Society for Microbiology, Washington, D.C., 1974, pp 431-435

2. Ashken MH, Cotton RE: Tropical skeletal muscle abscesses (pyomyositis tropicans). Br J Surg 50:846-852, May 1963

3. Cook J: Pyomyositis. East Afr Med J 40:574-579, Nov 1963

4. Foster WD: The bacteriology of tropical pyomyositis in Uganda. J Hyg (Camb) 63:517-524, Dec 1965

5. Levin MJ, Gardner P, Waldvogel FA: "Tropical" pyomyositis. An unusual infection due to *Staphylococcus aureus*. N Engl J Med 284:196-198, Jan 28, 1971

6. Cluff LE, Reynolds RC, Page DL, et al: Staphylococcal bacteremia and altered host resistance. Ann Intern Med 69:859-873, Nov 1968

7. Williams REO: Relation of antibiotic treatment to natural response to infection. J R Coll Physicians Lond 6:147-150, Jan 1972

8. Jawetz E, Gunnison JB, Coleman VR: The combined action of penicillin with streptomycin or Chloromycetin on enterococci in vitro. Science 111:254-256, Mar 10, 1950

9. Jawetz E, Sonne M: Penicillin-streptomycin treatment of enterococcal endocarditis—A re-evaluation. N Engl J Med 274: 710-715, Mar 31, 1966

10. Sabath LD: Synergy of antibacterial substances by apparently known mechanisms, *In* Antimicrobial Agents and Chemotherapy—1967. American Society for Microbiology, Ann Arbor, Michigan, 1968, pp 210-217

11. Watanakunakorn C, Glotzbecker C: Enhancement of the effects of antistaphylococcal antibiotics by aminoglycosides. Antimicrob Agents Chemother 6:802-806, Dec 1974

12. Lambelin G: Evidence for the *in vivo* synergism between penicillin and kanamycin. Chemotherapy 17:356-363, 1972

13. Greenman R, Steigbigel R. Remington J: Combination antibiotic therapy in experimental staphylococcal infection, *In* Clinical Research, Volume XXII, abstract submitted to the Annual Meeting, Western Section, The American Federation for Clinical Research, Feb 1974, p 185A

14. Steigbigel NH, Casey JI, Heeter BJ: Combined activity of the penicillinase-resistant penicillins and aminoglycosides against *Staph. aureus, In* Clinical Research, Volume XXI, Dec 1973, abstract submitted to the Annual Meeting, Eastern Section, The American Federation for Clinical Research, Jan 1974, p 976

15. Jawetz E, Gunnison JB, Speck RS, et al: Studies on antibiotic synergism and antagonism. AMA Arch Intern Med 87:349-359, Mar 1951

16. Lepper MH, Dowling HF: Treatment of pneumococcic meningitis with penicillin compared with penicillin plus aureomycin—Studies including observations on an apparent antagonism between penicillin and aureomycin. AMA Arch Intern Med 88: 489-494, Oct 1951

17. Taylor JF, Henderson BF: Tropical myositis, *In* Shaper AG, Kibukamusoke JW, Hutt MSF (Eds): Medicine in a Tropical Environment, British Medical Association, London, 1972, pp 32-44